HERBAL ALLIES FOR LIVER PROTECTION

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ABSTRACT

The liver is one of the main sites of metabolism, also synthesis the molecules needs for blood coagulation, transportation of fats etc. Most of the toxins like CCl₄, paracetamol, ethanol, Aflatoxins causes the liver damages like cirrhosis, fibrosis, scare formation due to lipid peroxidation and other oxidative damage. The states of liver are identified by elevating some biochemical parameters like ALT, AST, ALP, Total Bilirubin etc. Thus, to maintain healthy liver is crucible factor for overall health and well being. Synthetic drugs causes very much side effect so for avoiding that effect, the developed and developing countries mostly depend on traditional medicinal system from last few decades. Silymarine is most active constituent which are used in hepatitis and this are obtain from herbs “Milk Thistle”. So medicinal plants based new antihepatotoxins or hepatoprotective compound is used in alleviation of liver dysfunctions or as simple adjuncts to existing allopathic therapies.
Introduction:-

The liver is the key organ regulating homeostasis in the body. It is involved with almost all the biochemical pathways related to growth, fight against disease, nutrient supply, energy provision and reproduction (Sahani et al., 1999). The liver is expected not only to perform physiological functions but also to protect against the hazards of harmful drugs and chemicals. Inspite of tremendous scientific advancement in the field of hepatology in recent years, liver problems are on the rise. Jaundice and hepatitis are two major hepatic disorders that account for a high death rate (Pang et al., 1992).

Liver is one of the main sites of metabolism and also has a significant role through its various functions. It can split fats and proteins into smaller substances so that the cells of other tissues can use them for energy. Liver also synthesizes molecules needed for blood coagulation, transport of fats, conferring immunity to infection and many other purposes. Liver is capable of storing large quantities of fats, carbohydrates and even proteins and then latter releasing these nutrients into the tissue, which need them. Liver diseases are mainly caused by toxic chemicals, excess consumption of alcohol, infections and autoimmune disorders. Hence any liver disease can cause major physiological problems with grave consequences (Subramanian et al., 1998). Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages (Recknagel et al., 1983). Chronic liver injury, often leads to fibrosis, cirrhosis, scar formation. Thus, to maintain a healthy liver is a crucial factor for overall health and well being. About 20,000 deaths found every year due to liver disorders.

Physician and patients are in need of effective therapeutic agents with a low incident of side effects (Scote 1998). There is few effective plants that cure liver disease. So a considerable interest have developed in the examination of those numerous world wide traditional plant remedies which are useful for such treatment and that in recent years investigation carried out to provide experimental evidence which conforms that many of these plants do indeed have antihepatotoxic properties (Handa et al, 1986). So plants traditionally used in the alleviation of liver dysfunctions might therefore provide a useful source of new hepatoprotective compounds for development as pharmaceutical entities or as simple adjuncts to existing therapies (Scote 1998) with this perspective the present study is undertaken to evaluate the antihepatotoxic effect as medicinal plant. Herbs Commonly Used to Treat Hepatitis is “Milk Thistle”. According to NCCAM, milk thistle originally comes from Europe where it has been used as a treatment for liver disease and jaundice since the 16th century. It is now found throughout Europe, Asia and North America. Its scientific name is Silybum marianum. The ingredient believed to be responsible for its medicinal qualities is called silymarin. Silymarin is found in the fruits of the milk thistle plant. Silymarin is made up of three parts: silybin, silidianin and silicristin. Silybin is the most active ingredient and is believed responsible for the benefits attributed to silymarin (Pares et. al, 1998).
In Vivo Models of hepatotoxicity:

1. **CCl₄ Induced hepatotoxicity:**

CCl₄-induced liver damage was modeled in monolayer cultures of rat primary hepatocytes with a focus on involvement of covalent binding of CCl₄ metabolites to cell components and peroxidative damage as the cause of injury. Covalent binding of ¹⁴C-labeled metabolites was detected in hepatocytes immediately after exposure to CCl₄. Low oxygen partial pressure increased the reductive metabolism of CCl₄ and thus covalent binding. [¹⁴C]-CCl₄ was bound to lipids and to proteins throughout subcellular fractions. Binding occurred preferentially to triacylglycerols and phospholipids, with phosphatidylcholine containing the highest amount of label. The lipid peroxidation potency of CCl₄ revealed subtle differences compared to other peroxidative substances, viz., ADP-Fe³⁺ and cumol hydroperoxide, respectively. CCl₄, but not the other peroxidative substances, decreased the rate of triacylglycerol secretion as very low density lipoproteins. The anti-oxidant vitamin E (α-tocopherol) blocked lipid peroxidation, but not covalent binding, and secretion of lipoproteins remained inhibited. The radical scavenger piperonyl butoxide prevented CCl₄-induced lipid peroxidation as well as covalent binding of CCl₄ metabolites to cell components, and also restored lipoprotein metabolism. The results confirm that covalent binding of the CCl₃* radical to cell components initiates the inhibition of lipoprotein secretion and thus steatosis, whereas reaction with oxygen, to form CCl₃-OO*, initiates lipid peroxidation. The two processes are independent of each other, and the extent to which either process occurs depends on partial oxygen pressure. The former process may result in adduct formation and, ultimately, cancer initiation, whereas the latter results in loss of calcium homeostasis and, ultimately, apoptosis and cell death. (Meinrad et al. 2003, William et al. 1985)

2. **Paracetamol (acetaminophen) induced toxicity:**

In cases of paracetamol overdose, the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce NAPQI. As a result, hepatocellular supplies of glutathione become depleted, as the demand for glutathione is higher than its regeneration. NAPQI therefore remains in its toxic form in the liver and reacts with cellular membrane molecules, resulting in widespread hepatocyte damage and death, leading to acute hepatic necrosis. In animal studies, hepatic glutathione must be depleted to less than 70% of normal levels before hepatotoxicity occurs (Laura et al. 2003, Rannug et al. 1995).
3. Ethanol induced hepatotoxicity

A central role in the toxicity of alcohol may be played by acetaldehyde itself. The liver converts acetaldehyde into acetic acid by using Acetaldehyde dehydrogenase enzyme. If acetaldehyde is not efficiently converted into acetic acid (the second step in the metabolism of alcohol), severe toxicity can result which inhibiting the mitochondria reactions and functions. The alcoholic is a victim of a vicious circle: a high acetaldehyde level impairs mitochondria function, metabolism of acetaldehyde to acetic acid decreases, more acetaldehyde accumulates, and causes further liver damage--hepatitis and cirrhosis (Helmut et al.2005).

4. Nimesulide Induced hepatotoxicity:

Nimsulide is widely used as non-steroidal anti-inflammatory drug (NASID), is only weakly acidic and at the therapeutic doses, is a selective cyclooxygenase - 2 (COX-2) inhibitor, with only residual activity against COX-1. It is almost metabolize by liver. So, individuals with hepatic insufficiency, and with genetic or acquired abnormalities in drug-metabolizing enzymes, or trans-membrane carriers, may be at and increased risk of higher nimulide concentration in liver. Nimsulide is reported to causes injury to hepatic cells, mediated mainly by the impairment of ATP production by mitochondria. It also causes necrosis and cirrhosis due to generation of reactive oxygen species (ROS), which causes damage to tissues (Mary et.al 2006, Bissoli F 2008.)

5. Aflatoxin B1 Induced Hepatotoxicity:

Aflatoxins are produced by fungi of the genus Aspergillus, particularly A. flavus, A. parasiticus and A. nomius. Seventeen metabolites have been identified as aflatoxins, with aflatoxin B1 (AFB1) being the most commonly found metabolite in cereals and the one that exhibits the highest toxigenic effects [Leeson et.al. 1995]. Biochemically, aflatoxins affect energy, carbohydrates and lipids, nucleic acids and protein metabolism. Their biological effects include carcinogenicity, mutagenicity, teratogenicity and hepatotoxicity. Aflatoxins are a frequent problem for poultry production resulting in poor bird performance, which is caused by several factors including reduced activity of pancreatic enzymes, decreased concentration of bile, increased incidence of leg problems, injury to the sciatic nerve, and antagonism in the metabolism of vitamins, proteins and amino acids, lipids and carbohydrates, and damage to DNA (Eliana et.al. 2010).
6. Cadmium induced Toxicity:

Several studies have demonstrated that Cd modulate toxic effects operate through oxidative stress mechanisms. Oxidative stress, due to excessive production of reactive oxygen species (ROS), can damage tissues and cells by alteration of lipid peroxidation and protein or nucleic acid structure and function. Macrophages, participate in immune and inflammatory responses (Auger and Ross, 1992; Ramirez and, when they are activated, they secrete higher amounts of cytokines, ROS, reactive nitrogen species and several oxidized lipid mediators, e.g. eicosanoids and platelet activator factor, which contribute to tissue damage (Newairy et. al. 2007)

Liver function Test:-

Liver function tests are groups of clinical biochemistry laboratory blood assays designed to give information about the state of a liver. The parameters measured include SGPT/ALP, SGOT/AST, ALP, Albumin, Globulin, Total protein; Total Bilirubin are NOT liver function tests but are biomarkers of liver injury with some degree of intact liver function. (Rahul P. 2001)

1. Aminotransferases:

The aminotransferases (transaminases) are the most frequently utilized and specific indicators of hepatocellular necrosis. These enzymes Apartate Aminotransferase (AST) or serum glutamate oxaloacetic transaminase (SGOT) and Alanine Amino Transferase(ALT), formerly serum glutamic pyruvate transaminase (SGPT) catalyze the transfer of the amino acids of aspartate and alanine respectively to the keto group of ketoglutaric acid. ALT is primarily localized to the liver but the AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver. Whereas the AST is present in both the mitochondria and cytosol of hepatocytes, ALT is localized to the cytosol (Limdi et. al. 2003).

AST : alanine + α ketoglutarate = oxaloacetate + glutamate

ALT: alanine + α ketoglutarate = pyruvate + glutamate

Large increases in mitochondrial AST occur in serum after extensive tissue necrosis. Because of this, assay of mitochondrial AST have been advocated in myocardial infarction. Mitochondrial AST is also increased in chronic liver disease (Thapa et.al. 2007).
2. Alkaline Phosphatase:

Alkaline phosphatases are a family of zinc metaloenzymes, with a serine at the active center; they release inorganic phosphate from various organic orthophosphates and are present in nearly all tissues. Highest levels of alkaline phosphatase occur in cholestatic disorders. Elevations occur as a result of both intrahepatic and extrahepatic obstruction. Elevated serum levels of intestinal alkaline phosphatase have been found in cirrhosis and hepatitis (Shivaraj et.al. 2009).

3. Serum Bilirubin:

The source of 70 to 90% of bilirubin is decomposed hemoglobin of senescent erythrocytes. Hemoglobin is decomposed into globin and heme in the reticuloendothelial system, and the heme molecule loses its iron and ring-shaped structure to form bilirubin. The produced indirect (unconjugated) bilirubin undergoes glucuronide conjugation in the liver, and the formed direct (conjugated) bilirubin is secreted from the liver into the bile. The proportion of indirect bilirubin gradually increases in cases of liver cirrhosis or hepatic failure (Ghadi 2000).

4. Serum Proteins:

The liver is the major source of most the serum proteins. The parenchymal cells are responsible for synthesis of albumin, fibrinogen and other coagulation factors.

Albumin: Albumin is quantitatively the most important protein in plasma synthesized by the liver and is a useful indicator of hepatic function. Because the half life of albumin in serum is as long as 20 days, the serum albumin level is not a reliable indicator of hepatic protein synthesis in acute liver disease. The serum albumin levels are typically depressed in patients (Rahul P. 2001).

Prothrombin time: Prothrombin time reflects the activity of clotting factors produced in hepatocyte (factors I, II, V, VII, IX, and X). Since the half-lives of these clotting factors are as short as several hours to several days, the examination of prothrombin time is extremely helpful in the evaluation of hepatic reserve, even when the disease is progressing rapidly. Prothambin time decreases in the hepatic failure conditions (Hirohito et.al 2010).

Medicinal Plant used as antihepatotoxic:-
<table>
<thead>
<tr>
<th>Sr No</th>
<th>Biological source</th>
<th>Part used</th>
<th>Family</th>
<th>Models</th>
<th>Type of extract</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Platycodi radix</em></td>
<td>roots</td>
<td>Campanulaceae</td>
<td>CCl₄</td>
<td>Aqueous</td>
<td>Jeong et.al. (2002)</td>
</tr>
<tr>
<td>2</td>
<td><em>Coriandrum sativum</em></td>
<td>leaves</td>
<td>Umbelifere</td>
<td>CCl₄</td>
<td>ethanol: water (7:3)</td>
<td>Sreelatha et.al (2009)</td>
</tr>
<tr>
<td>3</td>
<td><em>Aerva lanata</em></td>
<td>Whole plants</td>
<td>Amaranthaceae</td>
<td>CCl₄</td>
<td>petroleum ether 60–80°C</td>
<td>Vijayam et.al (2005)</td>
</tr>
<tr>
<td>4</td>
<td><em>Pueraria tuberosa</em></td>
<td>Tubers</td>
<td>Fabaceae</td>
<td>Paracetamol</td>
<td>Methanolic</td>
<td>Yamin et.al (2010)</td>
</tr>
<tr>
<td>5</td>
<td><em>Zingiber officinale</em></td>
<td>Rhizomes</td>
<td>Zingiberacea</td>
<td>Paracetamol</td>
<td>50% ethanolic</td>
<td>Ajit et.al (2007)</td>
</tr>
<tr>
<td>6</td>
<td><em>Solanum fastigiatum</em></td>
<td>leaves</td>
<td>Solanaceae</td>
<td>Paracetamol</td>
<td>Aqueous</td>
<td>Sabi et.al (2008)</td>
</tr>
<tr>
<td>7</td>
<td><em>Hemidesmus indicus</em></td>
<td>Root</td>
<td>Asclepiadaceae</td>
<td>Ethanol</td>
<td>Ethanolic</td>
<td>Nadana et.al (2007)</td>
</tr>
<tr>
<td>8</td>
<td><em>Trigonella foenum graecum</em></td>
<td>Seeds</td>
<td>Fabaceae</td>
<td>Ethanol</td>
<td>Methanol</td>
<td>Kaviarasan et.al (2008)</td>
</tr>
<tr>
<td>9</td>
<td><em>Phyllanthus amarus</em></td>
<td>Aerial</td>
<td>Euphorbiaceae</td>
<td>Ethanol</td>
<td>Aqueous</td>
<td>Pramyothi et.al (2007)</td>
</tr>
<tr>
<td>10</td>
<td><em>Phyllanthus niruri</em></td>
<td>leaves and stems</td>
<td>Euphorbiaceae</td>
<td>Nimesulide</td>
<td>Aqueous</td>
<td>Sarka et.al (2005)</td>
</tr>
<tr>
<td>11</td>
<td><em>Trianthema portulacastrum</em></td>
<td>Leaves</td>
<td>Aizoaceae</td>
<td>Aflatoxin</td>
<td>Ethanol</td>
<td>Banu et.al (2009)</td>
</tr>
<tr>
<td>12</td>
<td><em>Hibiscus sabdarifffa</em></td>
<td>Flowers</td>
<td>Malvaceae</td>
<td>Cadmium</td>
<td>Aqueous</td>
<td>Asagba et.al (2007)</td>
</tr>
</tbody>
</table>

**References:**
14. Leeson, S, Diaz, G.J.; Summers, J.D. Poultry Metabolic Disorders and Mycotoxins; University Books: Guelph, Canada, 1995


